

Claims:

1. A combinatorial library of indolinone compounds, comprising at least ten indolinones that can be formed by reacting oxindoles with aldehydes.

5 2. The combinatorial library of claim 1 wherein said oxindoles are type A oxindoles.

3. The combinatorial library of claim 1 wherein said aldehydes are type B aldehydes.

4. A method of making an indolinone comprising the steps of

(a) creating a combinatorial library of indolinones by reacting a series of oxindoles with a series of aldehydes,

(b) testing said indolinones in biological assays,

15 (c) selecting one or more indolinones with favorable activity; and

(d) synthesizing one or more of said indolinones selected in step (c).

5. A 3-[(indole-3-yl)methylene]-2-indolinone compound having a substituent at the 1' position of the indole, where the substituent at the 1' position is selected from the group consisting of,

20 (a) alkyl that is optionally substituted with a monocyclic or bicyclic five, six, eight, nine, or ten membered heterocyclic ring, where the ring is optionally

substituted with one or more halogen, aldehyde, or trihalomethyl substituents;

5 (b) five, six, eight, nine, or ten membered monocyclic or bicyclic heterocyclic ring, where the ring is optionally substituted with one or more halogen or trihalomethyl substituents;

(c) an aldehyde or ketone of formula $-\text{CO}-\text{R}_{12}$, where R_{12} is selected from the group consisting of hydrogen, alkyl, and a five or six membered heterocyclic ring;

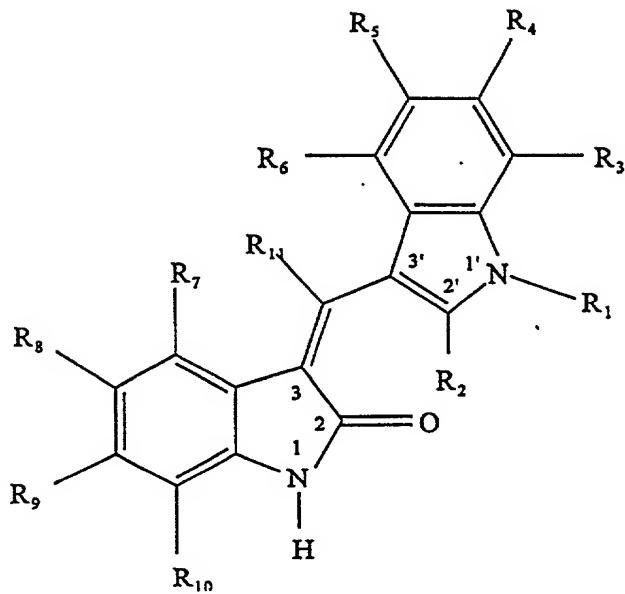
(d) a carboxylic acid of formula $-(\text{R}_{13})^n\text{-COOH}$ or ester of formula $-(\text{R}_{14})^m\text{-COO}-\text{R}_{15}$, where R_{13} , R_{14} , and R_{15} are independently selected from the group consisting of alkyl and a five or six membered heterocyclic ring and m and n are independently 0 or 1;

(e) a sulfone of formula $-(\text{SO}_2)-\text{R}_{16}$, where R_{16} is selected from the group consisting of alkyl and a five or six membered heterocyclic ring, where the ring is optionally substituted with an alkyl moiety;

(f) $-(\text{R}^{17})^n-(\text{indole-1-yl})$ or $-(\text{R}_{18})^m\text{-CHOH}-(\text{R}_{19})^p-(\text{indole-1-yl})$, where the indol moiety is optionally substituted with an aldehyde and R_{17} , R_{18} , and R_{19} are alkyl and m , n , and p are independently 0 or 1; and

(g) taken together with a 2' substituent of the indole ring forms a tricyclic moiety, where each ring in the tricyclic moiety is a five or six membered heterocyclic ring.

6. The compound, salt, isomer, metabolite, ester, amide, or prodrug of claim 5, wherein said compound has the formula,



5 where (a) R_1 is selected from the group consisting of,
(i) alkyl that is optionally substituted with a monocyclic or bicyclic five, six, eight, nine, or ten membered heterocyclic ring, where the ring is optionally substituted with one or more halogen, aldehyde, or
10 trihalomethyl substituents;
(ii) five, six, eight, nine, or ten membered monocyclic or bicyclic heterocyclic ring, where the ring

is optionally substituted with one or more halogen or trihalomethyl substituents;

5 (iii) an aldehyde or ketone of formula -CO-R₁₂, where R₁₁ is selected from the group consisting of hydrogen, alkyl, or a five or six membered heterocyclic ring;

10 (iv) a carboxylic acid of formula -(R₁₃)_n-COOH or ester of formula -(R₁₄)_m-COO-R₁₅, where R₁₃, R₁₄, and R₁₅ and are independently selected from the group consisting of alkyl or a five or six membered heterocyclic ring and n and m are independently 0 or 1;

15 (v) a sulfone of formula -(SO₂)-R₁₆, where R₁₆ is selected from the group consisting of alkyl or a five or six membered heterocyclic ring, where the ring is optionally substituted with an alkyl moiety;

20 (vi) -(R₁₇)_n-(indole-1-yl) or -(R₁₈)_m-CHOH-(R₁₉)_p-(indole-1-yl), where the indol moiety is optionally substituted with an aldehyde and R₁₇, R₁₈, and R₁₉ are alkyl and n, m, and p are independently 0 or 1;

25 (vii) taken together with a 2' substituent of the indole ring forms a tricyclic moiety, where each ring in the tricyclic moiety is a five or six membered heterocyclic ring;

(b) R₂, R₃, R₄, R₅, and R₆ are selected from the group consisting of,

25 (i) hydrogen or alkyl that is optionally substituted with a monocyclic or bicyclic five, six, eight, nine, or ten membered heterocyclic ring, where the

ring is optionally substituted with one or more halogen, aldehyde, or trihalomethyl substituents;

5 (ii) five, six, eight, nine, or ten membered monocyclic or bicyclic heterocyclic ring, where the ring is optionally substituted with one or more halogen or trihalomethyl substituents;

(iii) an aldehyde or ketone of formula -CO-R₂₀, where R₂₀ is selected from the group consisting of hydrogen, alkyl, or a five or six membered heterocyclic ring;

10 (iv) a carboxylic acid of formula -(R₂₁)_n-COOH or ester of formula -(R₂₂)-COO-R₂₃, where R₂₁, R₂₂, and R₂₃ and are independently selected from the group consisting of alkyl or a five or six membered heterocyclic ring and m and n are independently 0 or 1;

15 (v) halogen or an alcohol of formula (R₂₄)_m-OH or an ether of formula -(R₂₄)_n-O-R₂₅, where R₂₄ and R₂₅ are independently selected from the group consisting of alkyl and a five or six membered heterocyclic ring and m and n are independently 0 or 1;

20 (vi) -NR₂₆R₂₇, where R₂₆ and R₂₇ are independently selected from the group consisting of hydrogen, oxygen, alkyl, and a five or six membered heterocyclic ring; or -NHCOR₂₈, where R₂₈ is selected from the group consisting of hydroxyl, alkyl, and a five or six membered heterocyclic ring, where the ring is optionally substituted with alkyl, halogen, carboxylate, or ester;

(vii) $-\text{SO}_2\text{NR}_{29}\text{R}_{30}$, where R_{29} and R_{30} are selected from the group consisting of hydrogen, oxygen, alkyl, and a five or six membered heterocyclic ring;

5 (viii) any two of R_3 , R_4 , R_5 , or R_6 taken together form a bicyclic or tricyclic heterocyclic moiety fused to the six membered ring of the indole, where each ring in the multicyclic moiety is a five or six membered heterocyclic ring;

(c) R_7 , R_8 , R_9 , and R_{10} are independently selected from the group consisting of,

(i) hydrogen or alkyl that is optionally substituted with a monocyclic or bicyclic five, six, eight, nine, or ten membered heterocyclic ring, where the ring is optionally substituted with one or more halogen, aldehyde, or trihalomethyl substituents;

(ii) five, six, eight, nine, or ten membered monocyclic or bicyclic heterocyclic ring, where the ring is optionally substituted with one or more halogen or trihalomethyl substituents;

20 (iii) an aldehyde or ketone of formula $-\text{CO}-\text{R}_{31}$, where R_{31} is selected from the group consisting of hydrogen, alkyl, or a five or six membered heterocyclic ring;

25 (iv) a carboxylic acid of formula $-(\text{R}_{32})^n\text{COOH}$ or ester of formula $-(\text{R}_{33})^m\text{COO}-\text{R}_{34}$, where R_{32} , R_{33} , and R_{34} and are independently selected from the group consisting of alkyl or a five or six membered heterocyclic ring and n and m are independently 0 or 1;

(v) halogen or an alcohol of formula $(R_{35})^m-OH$ or an ether of formula $-(R_{35})^n-O-R_{36}$, where R_{35} and R_{36} are independently chosen from the group consisting of alkyl or a five or six membered heterocyclic ring and m and n are independently 0 or 1;

(vi) $-NR_{37}R_{38}$, where R_{37} and R_{38} are independently selected from the group consisting of hydrogen, oxygen, alkyl, and a five or six membered heterocyclic ring; or $-NHCOR_{39}$, where R_{39} is selected from the group consisting of hydroxyl, alkyl, and a five or six membered heterocyclic ring, where the ring is optionally substituted with alkyl, halogen, carboxylate, or ester;

(vii) $-SO_2NR_{40}R_{41}$, where R_{40} and R_{41} are selected from the group consisting of hydrogen, oxygen, alkyl, and a five or six membered heterocyclic ring;

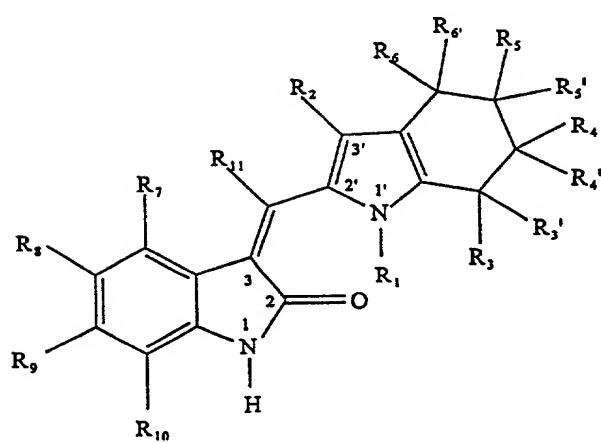
(viii) any two of R_7 , R_8 , R_9 , or R_{10} taken together form a bicyclic or tricyclic heterocyclic moiety fused to the six membered ring of the indole, where each ring in the multicyclic moiety is a five or six membered heterocyclic ring; and

(d) R_{11} is hydrogen or alkyl;
provided that at least one of R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , or R_{10} is alkyl or provided that at least four of R_1 , R_2 , R_3 , R_4 , R_5 , or R_6 are not hydrogen.

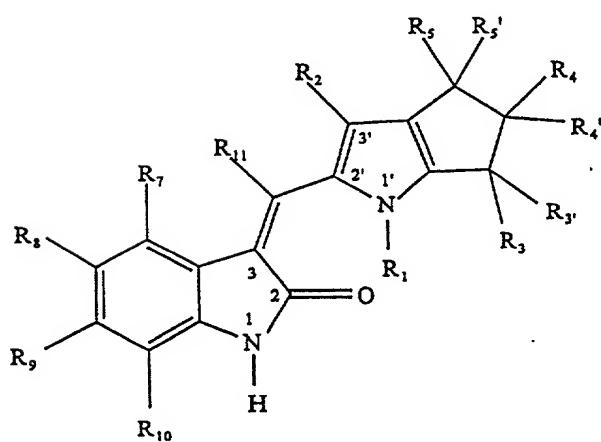
25 7. An optionally substituted 3-[(tetrahydroindole-2-yl)methylene]-2-indolinone or 3-[(cyclopentano-b-pyrrol-2-yl)methylene]-2-indolinone compound.

8. The indolinone compound of claim 7 of formula XIX or XX,

XIX



XX



or a pharmaceutically acceptable salt, isomer, metabolite, ester, amide, or prodrug thereof

where (a) R_1 is selected from the group consisting of,

5 (i) alkyl that is optionally substituted with a monocyclic or bicyclic five, six, eight, nine, or ten membered heterocyclic ring, where the ring is optionally substituted with one or more halogen, or trihalomethyl substituents;

10 (ii) five, six, eight, nine, or ten membered monocyclic or bicyclic heterocyclic ring, where the ring is optionally substituted with one or more halogen or trihalomethyl substituents;

15 (iii) ketone of formula $-CO-R_{12}$, where R_{11} is selected from the group consisting of hydrogen, alkyl, or a five or six membered heterocyclic ring;

20 (iv) a carboxylic acid of formula $-(R_{13})_n-COOH$ or ester of formula $-(R_{14})_m-COO-R_{15}$, where R_{13} , R_{14} , and R_{15} and are independently selected from the group consisting of alkyl or a five or six membered heterocyclic ring and n and m are independently 0 or 1;

25 (v) a sulfone of formula $-(SO_2)-R_{16}$, where R_{16} is selected from the group consisting of alkyl or a five or six membered heterocyclic ring, where the ring is optionally substituted with an alkyl moiety;

(vi) $-(R_{17})_n-(indole-1-yl)$ or $-(R_{18})_m-CHOH-(R_{19})p-(indole-1-yl)$, where the indolemoiety is optionally substituted with an aldehyde and R_{17} , R_{18} , and R_{19} are alkyl and n , m , and p are independently 0 or 1;

(vii) taken together with a 2' substituent of the indole ring forms a tricyclic moiety, where each ring in the tricyclic moiety is a five or six membered heterocyclic ring;

5 (b) R_2 , R_3 , R_3' , R_4 , R_4' , R_5 , R_5' , R_6 and R_6' are selected from the group consisting of,

(i) hydrogen;

10 (ii) alkyl that is optionally substituted with a monocyclic or bicyclic five, six, eight, nine, or ten membered heterocyclic ring, where the ring is optionally substituted with one or more halogen, or trihalomethyl substituents;

15 (iii) five, six, eight, nine, or ten membered monocyclic or bicyclic heterocyclic ring, where the ring is optionally substituted with one or more halogen or trihalomethyl substituents;

20 (iv) ketone of formula $-CO-R_{20}$, where R_{20} is selected from the group consisting of hydrogen, alkyl, or a five or six membered heterocyclic ring;

25 (v) a carboxylic acid of formula $-(R_{21})_n-COOH$ or ester of formula $-(R_{22})_m-COO-R_{23}$, where R_{21} , R_{22} , and R_{23} and are independently selected from the group consisting of alkyl or a five or six membered heterocyclic ring and m and n are independently 0 or 1;

(vi) halogen;

(vii) an alcohol of formula $(R_{24})_n-OH$ or an ether of formula $-(R_{24})_n-O-R_{25}$, where R_{24} and R_{25} are independently selected from the group consisting of alkyl and a five or

six membered heterocyclic ring and m and n are independently 0 or 1;

5 (viii) $-\text{NR}_{26}\text{R}_{27}$, where R_{26} and R_{27} are independently selected from the group consisting of hydrogen, oxygen, alkyl, and a five or six membered heterocyclic ring;

(ix) $-\text{NHCOR}_{28}$, where R_{28} is selected from the group consisting of hydroxyl, alkyl, and a five or six membered heterocyclic ring, where the ring is optionally substituted with alkyl, halogen, carboxylate, or ester;

(x) $-\text{SO}_2\text{NR}_{29}\text{R}_{30}$, where R_{29} and R_{30} are selected from the group consisting of hydrogen, oxygen, alkyl, and a five or six membered heterocyclic ring;

15 (xi) any two of R_3 , R_3' , R_4 , R_4' , R_5 , R_5' , R_6 , or R_6' taken together form a bicyclic or tricyclic heterocyclic moiety fused to the six membered ring of the indole, where each ring in the multicyclic moiety is a five or six membered heterocyclic ring;

20 (c) R_7 , R_8 , R_9 , and R_{10} are independently selected from the group consisting of,

(i) hydrogen;

25 (ii) alkyl that is optionally substituted with a monocyclic or bicyclic five, six, eight, nine, or ten membered heterocyclic ring, where the ring is optionally substituted with one or more halogen, or trihalomethyl substituents;

(iii) five, six, eight, nine, or ten membered monocyclic or bicyclic heterocyclic ring, where the ring

is optionally substituted with one or more halogen or trihalomethyl substituents;

(iv) ketone of formula $-\text{CO}-\text{R}_{31}$, where R_{31} is selected from the group consisting of hydrogen, alkyl, or a five or six membered heterocyclic ring;

(v) a carboxylic acid of formula $-(\text{R}_{32})_n-\text{COOH}$ or ester of formula $-(\text{R}_{33})_m-\text{COO}-\text{R}_{34}$, where R_{32} , R_{33} , and R_{34} and are independently selected from the group consisting of alkyl or a five or six membered heterocyclic ring and n and m are independently 0 or 1;

(vi) halogen;

(vii) an alcohol of formula $(\text{R}_{35})_m-\text{OH}$ or an ether of formula $-(\text{R}_{35})_n-\text{O}-\text{R}_{36}$, where R_{35} and R_{36} are independently chosen from the group consisting of alkyl or a five or six membered heterocyclic ring and m and n are independently 0 or 1;

(viii) $-\text{NR}_{37}\text{R}_{38}$, where R_{37} and R_{38} are independently selected from the group consisting of hydrogen, oxygen, alkyl, and a five or six membered heterocyclic ring;

(ix) $-\text{NHCOR}_{39}$, where R_{39} is selected from the group consisting of hydroxyl, alkyl, and a five or six membered heterocyclic ring, where the ring is optionally substituted with alkyl, halogen, carboxylate, or ester;

(x) $-\text{SO}_2\text{NR}_{40}\text{R}_{41}$, where R_{40} and R_{41} are selected from the group consisting of hydrogen, oxygen, alkyl, and a five or six membered heterocyclic ring;

(xi) any two of R_7 , R_8 , R_9 , or R_{10} taken together form a bicyclic or tricyclic heterocyclic moiety fused to

the six membered ring of the indole, where each ring in the multicyclic moiety is a five or six membered heterocyclic ring; and

(d) R_{11} is hydrogen or alkyl

5 9. An indolinone compound having a substituent at the 5 position of the oxindole ring, where the substituent at the 5 position of the oxindole ring is selected from the group consisting of

10 (a) alkyl that is optionally substituted with a monocyclic or bicyclic five, six, eight, nine, or ten membered heterocyclic ring, where the ring is optionally substituted with one or more halogen, or trihalomethyl substituents;

15 (b) five, six, eight, nine, or ten membered monocyclic or bicyclic heterocyclic ring, where the ring is optionally substituted with one or more halogen or trihalomethyl substituents;

20 (c) a ketone of formula $-CO-R_{10}$, where R_{10} is selected from the group consisting of hydrogen, alkyl, or a five or six membered heterocyclic ring;

25 (d) a carboxylic acid of formula $-(R_{11})^n-COOH$ or ester of formula $-(R_{12})-COO-R_{13}$, where R_{11} , R_{12} , and R_{13} and are independently selected from the group consisting of alkyl or a five or six membered heterocyclic ring and m and n are independently 0 or 1;

(e) halogen;

(f) an alcohol of formula $(R_{14})^m-OH$ or an ether of formula $-(R_{14})^n-O-R_{15}$, where R_{14} and R_{15} are independently selected from the group consisting of alkyl and a five or six membered heterocyclic ring and m and n are independently 0 or 1;

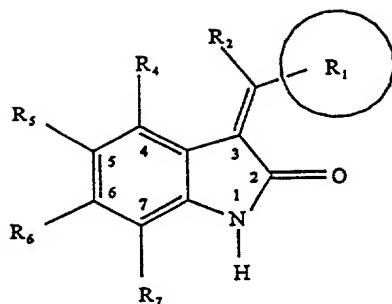
(g) $-NR_{16}R_{17}$, where R_{16} and R_{17} are independently selected from the group consisting of hydrogen, alkyl, and a five or six membered heterocyclic ring;

(h) $-NHCOR_{18}$, where R_{18} is selected from the group consisting of alkyl, and a five or six membered heterocyclic ring, where the ring is optionally substituted with alkyl, halogen, carboxylate, or ester;

(i) $-SO_2NR_{19}R_{20}$, where R_{19} and R_{20} are selected from the group consisting of hydrogen, alkyl, and a five or six membered heterocyclic ring;

(j) any two of R_4 , R_5 , R_6 , or R_7 , taken together form a bicyclic or tricyclic heterocyclic moiety fused to the six membered ring of the oxindole, where each ring in the multicyclic moiety is a five or six membered heterocyclic ring.

10. The compound of claim 9 of the following formula,



where (a) R_5 is selected from the group consisting of,

(i) alkyl that is optionally substituted with a monocyclic or bicyclic five, six, eight, nine, or ten membered heterocyclic ring, where the ring is optionally substituted with one or more halogen, or trihalomethyl substituents;

(ii) five, six, eight, nine, or ten membered monocyclic or bicyclic heterocyclic ring, where the ring is optionally substituted with one or more halogen or trihalomethyl substituents;

(iii) a ketone of formula $-CO-R_{10}$, where R_{10} is selected from the group consisting of hydrogen, alkyl, or a five or six membered heterocyclic ring;

(iv) a carboxylic acid of formula $-(R_{11})_n-COOH$ or ester of formula $-(R_{12})_m-COO-R_{13}$, where R_{11} , R_{12} , and R_{13} and are independently selected from the group consisting of alkyl or a five or six membered heterocyclic ring and m and n are independently 0 or 1;

(v) halogen;

(vi) an alcohol of formula $(R_{14})_m-OH$ or an ether of formula $-(R_{14})_n-O-R_{15}$, where R_{14} and R_{15} are independently

selected from the group consisting of alkyl and a five or six membered heterocyclic ring and m and n are independently 0 or 1;

5 (vii) -NR₁₆R₁₇, where R₁₆ and R₁₇ are independently selected from the group consisting of hydrogen, alkyl, and a five or six membered heterocyclic ring;

10 (viii) -NHCOR₁₈, where R₁₈ is selected from the group consisting of alkyl, and a five or six membered heterocyclic ring, where the ring is optionally substituted with alkyl, halogen, carboxylate, or ester;

15 (ix) -SO₂NR₁₉R₂₀, where R₁₉ and R₂₀ are selected from the group consisting of hydrogen, alkyl, and a five or six membered heterocyclic ring;

20 (x) any two of R₄, R₅, R₆, or R, taken together form a bicyclic or tricyclic heterocyclic moiety fused to the six membered ring of the oxindole, where each ring in the multicyclic moiety is a five or six membered heterocyclic ring;

25 (b) R₁ is selected from the group consisting of a five, six, eight, nine, and ten membered monocyclic or bicyclic heterocyclic ring, where the ring is optionally substituted with one or more substituents selected from the group consisting of

(i) hydrogen and alkyl that is optionally substituted with a monocyclic or bicyclic five, six, eight, nine, or ten membered heterocyclic ring, where the ring is optionally substituted with one or more halogen, or trihalomethyl substituents;

(ii) five, six, eight, nine, or ten membered monocyclic or bicyclic heterocyclic ring, where the ring is optionally substituted with one or more halogen or trihalomethyl substituents;

5 (iii) a ketone of formula -CO-R₂₁, where R₂₁ is selected from the group consisting of hydrogen, alkyl, or a five or six membered heterocyclic ring;

10 (iv) a carboxylic acid of formula -(R₂₂)_n-COOH or ester of formula -(R₂₃)-COO-R₂₄, where R₂₂, R₂₃, and R₂₄ and are independently selected from the group consisting of alkyl or a five or six membered heterocyclic ring and m and n are independently 0 or 1;

15 (v) halogen;

20 (vi) an alcohol of formula (R₂₅)_m-OH or an ether of formula -(R₂₅)_n-O-R₂₆, where R₂₅ and R₂₆ are independently selected from the group consisting of alkyl and a five or six membered heterocyclic ring and m and n are independently 0 or 1;

25 (vii) -NR₂₇R₂₈, where R₂₇ and R₂₈ are independently selected from the group consisting of hydrogen, alkyl, and a five or six membered heterocyclic ring;

25 (viii) -NHCOR₂₉, where R₂₉ is selected from the group consisting of alkyl, and a five or six membered heterocyclic ring, where the ring is optionally substituted with alkyl, halogen, carboxylate, or ester;

(ix) -SO₂NR₃₀R₃₁, where R₃₀ and R₃₁ are selected from the group consisting of hydrogen, alkyl, and a five or six membered heterocyclic ring;

(c) R_4 , R_6 , and R_7 are independently selected from the group consisting of,

(i) hydrogen and alkyl that is optionally substituted with a monocyclic or bicyclic five, six, eight, nine, or ten membered heterocyclic ring, where the ring is optionally substituted with one or more halogen, or trihalomethyl substituents;

(ii) five, six, eight, nine, or ten membered monocyclic or bicyclic heterocyclic ring, where the ring is optionally substituted with one or more halogen or trihalomethyl substituents;

(iii) a ketone of formula $-CO-R_{32}$, where R_{32} is selected from the group consisting of hydrogen, alkyl, or a five or six membered heterocyclic ring;

(iv) a carboxylic acid of formula $-(R_{33})_n-COOH$ or ester of formula $-(R_{34})_m-COO-R_{35}$, where R_{33} , R_{34} and R_{35} and are independently selected from the group consisting of alkyl or a five or six membered heterocyclic ring and m and n are independently 0 or 1;

(v) halogen;

(vi) an alcohol of formula $(R_{36})_m-OH$ or an ether of formula $-(R_{36})_n-O-R_{37}$, where R_{36} and R_{37} are independently selected from the group consisting of alkyl and a five or six membered heterocyclic ring and m and n are independently 0 or 1;

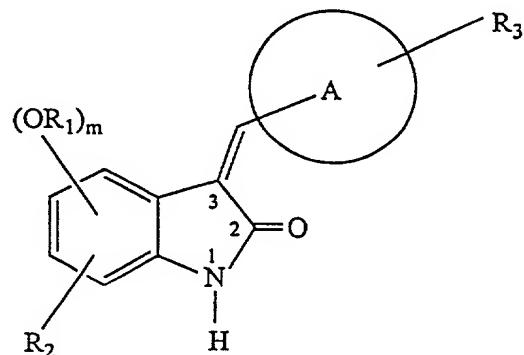
(vii) $-NR_{38}R_{39}$, where R_{38} and R_{39} are independently selected from the group consisting of hydrogen, alkyl, and a five or six membered heterocyclic ring;

(viii) $-\text{NHCOR}_{40}$, where R_{40} is selected from the group consisting of alkyl, and a five or six membered heterocyclic ring, where the ring is optionally substituted with alkyl, halogen, carboxylate, or ester;

5 (ix) $-\text{SO}_2\text{NR}_{41}\text{R}_{42}$, where R_{41} and R_{42} are selected from the group consisting of hydrogen, alkyl, and a five or six membered heterocyclic ring; and

(d) R_2 is hydrogen or alkyl.

11. A compound having formula XXI, wherein:



XXI

(a) A is a five or six membered ring comprised of atoms selected from the group consisting of oxygen, carbon, sulfur and nitrogen;

15 (b) m is zero, 1, or 2;

(c) R_1 is hydrogen, $\text{C}_1\text{-C}_6$ alkyl or $\text{C}_2\text{-C}_6$ alkanoyl;

(d) one of R_2 and R_3 independently is hydrogen and the other is a substituent selected from:

(1) a C_1 - C_6 alkyl group substituted by 1, 2 or 3 hydroxy groups;

(2) SO_3R_4 in which R_4 is hydrogen or C_1 - C_6 alkyl unsubstituted or substituted by 1, 2 or 3 hydroxy groups;

(3) SO_2NHR_5 in which R_5 is as R_4 defined above or a $-(CH_2)_n-N(C_1-C_6\text{ alkyl})_2$ group in which n is 2 or 3;

(4) $COOR_6$ in which R_6 is C_1 - C_6 alkyl unsubstituted or substituted by phenyl or by 1, 2 or 3 hydroxy groups or phenyl;

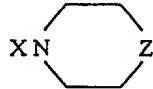
(5) $CONHR_7$, in which R_7 is hydrogen, phenyl or C_1 - C_6 alkyl substituted by 1, 2 or 3 hydroxy groups or by phenyl;

(6) $NHSO_2R_8$ in which R_8 is C_1 - C_6 alkyl or phenyl unsubstituted or substituted by halogen or by C_1 - C_4 alkyl;

(7) $N(R_9)_2$, NHR_9 , or OR_9 , wherein R_9 is C_2 - C_6 alkyl substituted by 1, 2 or 3 hydroxy groups;

(8) $NHCOR_{10}$, $OOCR_{10}$ or CH_2OOCR_{10} in which R_{10} is C_1 - C_6 alkyl substituted by 1, 2 or 3 hydroxy groups;

(9) $NHCONH_2$; $NH-C(NH_2)=NH$; $C(NH_2)=NH$; $CH_2NHC(NH_2)=NH$; CH_2NH_2 ; $OPO(OH)_2$; $CH_2OPO(OH)_2$; $PO(OH)_2$; or a



wherein X is selected from the group consisting of CH_2 , SO_2 , CO , or $NHCO(CH_2)_p$ in which p is 1, 2, or 3 and Z is CH_2 , O or $N-R_{11}$ in which R_{11} is hydrogen or is as R_9 defined above.

12. A method of making an indolinone compound of any one of claims 5-11 comprising the steps of reaching an appropriate aldehyde and oxindol and separating the indolinone from the aldehyde and oxindol reactants.

5 13. A pharmaceutical composition comprising (i) a pharmaceutically acceptable carrier or excipient and (ii) a compound according to any one of claims 5-11.

10 14. A method for treating a disease related to unregulated tyrosine kinase signal transduction, the method comprising the step of administering to a subject in need thereof a therapeutically effective amount of a compound according to any one of claims 5-11.

15 15. A method for regulating tyrosine kinase signal transduction comprising administering to a subject a therapeutically effective amount of a compound according to any one of claims 5-11.

20 16. A method of preventing or treating an abnormal condition in an organism, where the abnormal condition is associated with an aberration in a signal transduction pathway characterized by an interaction between a protein kinase and a natural binding partner, where the method comprises the following steps:

(a) administering a compound of any one of claims 5-11 to an organism; and

(b) promoting or disrupting the abnormal interaction.

17. A method of preventing or treating an abnormal condition in an organism, where the abnormal condition is associated with an aberration in a signal transduction pathway characterized by an interaction between a protein kinase and a natural binding partner, where the method comprises the following steps:

(a) administering a compound of any one of claims 5-11 to an organism; and

(b) promoting or disrupting the abnormal interaction.